

EXHIBIT P

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Nodular organization and differential intrametastatic distribution of the fluorescent dye Hoechst 33342 in B16 melanoma liver metastasis.

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The development of B16F10 liver metastases as related to its vascular organization was studied by morphological and functional methods, using the DNA-binding fluorochrome, Hoechst 33342. Experimental metastases were produced by intrasplenic injection of B16F10 melanoma cells, and the animals were sacrificed 3-7 days after tumor cell injection. The results show that early metastases are made up of avascular nodules of tumor cells, which subsequently developed lacunae which are not lined by endothelial cells and usually contain blood cells. A more developed metastasis seems to be made up of several nodules with or without lacunae. Between the nodules, vessels connected to blood circulation were usually observed. A functional study with a fluorescent dye showed that early metastases stained negatively, while more developed metastases showed a reticular fluorescent pattern, coincident with the intrametastatic vascular network and displaying a nodular image. In this case, the fluorescence displayed a gradient of intensity decreasing from the vessels towards the lacunae, where the tumor cells showed no fluorescence. In summary, our results suggest that B16 liver metastases have a nodular growth pattern, which is characterized by the formation, during their development, of lacunae not connected to the general circulation and that tumor cells have poor access to small molecules delivered from the blood.